ratio between 10:90 and 90:10 can be found on page 8, line 28 of the specification of the present application where the ratio is describe in terms of weight ("in a ratio (i):(ii) by weight) and original claim 23. Support for claim 25 can be found on page 5, lines 15-30 of the specification of the present invention.

The amendments to the claims are not narrowing and are made to expedite the prosecution by eliminating prolonged arguments over matters that are not of concern to our client regarding the patent application and are not directed to the patentability of the claims. They should therefore have no effect on the application of the doctrine of equivalents to the newly amended claims.

Claim Rejections - 35 U.S.C. Section 112, second paragraph

Claims 21-23 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Amendments to the claims have been made addressing the issues raised by the Examiner. The present set of claims are believed to be sufficiently definite to satisfy the dictates of 35 U.S.C. 112, second paragraph.

Claim Rejection - 35 U.S.C. 102

Claims 2-21 and 25 were rejected under 35 U.S.C. 102(b) as being anticipated by Sachs et al. (U.S. Patent No. 5,945,124). Claims 2-21 and 25 were rejected under 35 U.S.C. 102(e) as being anticipated by Sachs et al. (U.S. Patent No. 5,945,124) or Sachs et al. (U.S. Patent No. 6,068,865).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference", *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ.2d 1051, 1053 (Fed. Cir. 1987).

The present invention relates to a pellet comprising an acid labile benzimidazole compound, wherein the pellet comprises (a) an inert nucleus; (b) a layer disposed over said

inert nucleus, comprising an acid labile benzimidazole compound, an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients; (c) one or more intermediate layers that comprise: (i) an inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients; and (ii) a system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert polymer insoluble in water; said intermediate layer(s) (c) disposed over said layer that covers the inert nucleus; and (d) an external layer comprising an enteric coating disposed over said intermediate layer(s) (c).

U.S. Patent No. 5,945,124 and U.S. Patent No. 6,068,856 describe an oral pharmaceutical composition of pantoprazole in pellet form which contains an alkaline core with all or part of pantoprazole, an intermediate layer formed from a water insoluble release-slowing film former and an outer enteric coating.

The present invention is not anticipated by U.S. Patent No. 5,945,124 or by U.S. Patent No. 6,068,856 because the cited prior art does not describe one more or more intermediate layers that comprise an inert, non-alkaline coating formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients as defined in the present invention.

U.S. Patent No.'s 5,945,124 and 6,068,856 describe a release slowing intermediate layer as insoluble in water that has a release rate controlled by incorporating suitable water-soluble pore formers including HPMC, see col. 5, lines 48-51 of U.S. Patent No.'s 5,945,124 and 6,068,856. Therefore, U.S. Patent No.'s 5,945,124 and 6,068,856 do not teach or suggest the claim limitation of a pellet comprising one or more intermediate layers that comprise an inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients as defined in the claims of the present invention. This layer (c)(i) as defined in the claims of the present invention is not disclosed or suggested by U.S. Patent No.'s 5,945,124 and 6,068,856. The layer described in these patents is a "release slowing layer" not an inert, non-alkaline coating layer. It is further noted that Example I describes the release slowing layer as comprising ethylcellulose, lactose micronized, propylene glycol, and ammonia, see Example 1 on col. 6, lines 38-45 of U.S. Patent No.'s 5,945,124 and 6,068,856.

U.S. Patent No.'s 5,945,124 and 6,068,856 at col. 4, lines 3-6 and 51-52 disclose that the pantoprazole must be in an alkaline salt form or together with alkaline substances in the tablet or pellet form. Example 3 of U.S. Patent No.'s 5,945,124 and 6,068,856 describes the starter pellet as including NaOH, and the active pellet is prepared by spraying pantoprazole in the form of sodium salt together with NaOH, see Example 3 on col. 7, line 46 to col. 8, line 8 of U.S. Patent No. 5,945,124 and Example 3 on col. 7, line 36 to col. 8, line 2 of U.S. Patent No. 6,068,856. Example 4 of U.S. Patent No.'s 5,945,124 and 6,068,856 describes the active pellet as being prepared by mixing pantoprazole in the form of sodium salt with sodium carbonate, see col. 8, lines 21-40 of U.S. Patent No. 5,945,124 and Example 4 on col. 8, lines 3-21 of U.S. Patent No. 6,068,856. This is not required in the present invention.

Therefore it is clear that U.S. Patent No.'s 5,945,124 and 6,068,856 teach that in order to have a stable formulation of pantoprazole, the active ingredient has to be present in the tablet core or in pellets in the form of its alkaline salts or in direct or intimate mixture with alkaline substances, please see the Examples of U.S. Patent No.'s 5,945,124 and 6,068,856 where pantoprazole is present in the pellets as a sodium salt and/or intimately mixed with alkaline substances.

The present invention is, however, different from the teaching of U.S. Patent No.'s 5,945,124 and 6,068,856. The pellets of the present invention do not have the active compound, any acid labile benzimidazole compound, in the form of its alkaline salt, nor in direct or intimate contact with any alkaline compound. This is clearly reflected in the definition of claim 25 and in the description of the present application.

Thus, claim 25 of the present application defines the active compound as "an acid labile benzimidazole compound", there is no mention of any pharmaceutically alkaline salt present in the claim. Furthermore, lines 4-20 of page 4 of the description do not refer to such salts.

According to claim 25 of the present application, the benzimidazole compound which is added over an inert nucleus (a) to form layer (b) cannot be in contact with any alkaline compound since claim 25 clearly defines that the polymer soluble in water present in layer (b)

is non alkaline, and the other excipients are inert (see lines 33-34 of page 6 of the description where it is stated that "the term inert, applied to a polymer of an excipient, refers to the fact that said compounds do not react in the conditions used"). Finally, the pellets prepared in the examples of the present application do not contain any alkaline compound."

Therefore, U.S. Patent No.'s 5,945,124 and 6,068,856 do not teach each and every element as set forth in the claims of the present invention. It is respectfully requested that this rejection be withdrawn.

Claim Rejection 35 U.S.C. 103(a)

Claims 2-25 were rejected under 35 U.S.C. 103(a) as being unpatentable over Sachs et al. (U.S. Patent No. 5,945,124) or Sachs et al. (U.S. Patent No. 6,068,865).

The Examiner alleges that it would have been obvious to one skilled in the art at the time of the invention to provide mixtures of pellets having different release profiles in an effort to provide quicker release of the active agent while also providing prolonged release of the active agent. Applicants respectfully disagree.

Claims 2-21 and 25 where rejected under 35 U.S.C. 103(a) as being unpatentable over Sachs et al. (U.S. Patent No. 5,945,124) in view of Paradissis et al. (U.S. Patent No. 5,445,829) or Sachs et al. (U.S. Patent No. 6,068,865) in view of Paradissis et al. (U.S. Patent No. 5,445,829).

The Examiner alleges it would have been obvious to one skilled in the art at the time of the invention to combine the teachings of U.S. Patent No. 5,945,124 with U.S. Patent No. 5,445,829 or U.S. Patent No. 6,068,865 with U.S. Patent No. 5,445,829 with the expectation of providing a particular dose release profile that provides both a quick onset of action and a prolonged duration of action. Applicants respectfully disagree.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, USPQ 580 (CCPA 1974).

As stated above, the pellet of the present invention comprises an active layer disposed over an inert nucleus, comprising an acid labile benzimidazole compound, an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients.

The present invention is nonobvious over the cited prior art because U.S. Patent No. 5,945,124 or U.S. Patent No. 6,068,856 do not teach or suggest all the claim limitations of the present invention.

U.S. Patent No. 5,945,124 and U.S. Patent No. 6,068,856 disclose an oral pharmaceutical composition of pantoprazole, an acid labile benzimidazole compound, in pellet form which contains:

a) an alkaline core with all or part of pantoprazole;

b) an intermediate layer formed from a water-insoluble release-slowing film former; and

c) an outer enteric coating.

As mentioned above, the pantoprazole of U.S. Patent No. 5,945,124 and U.S. Patent No. 6,068,856 has to be present in the form of its alkaline salts or in direct or intimate mixture with alkaline substances in the tablet core or in pellets.

The present invention provides an alternative solid pharmaceutical formulation of modified release that contains an acid labile benzimidazole compound as an active ingredient, suitable for oral administration in terms of the stability of active compound in the stomach and in terms of reaching an effective concentration of said active compound in blood.

The alternative pharmaceutical formulation provided by the present invention comprises a number of modified release and gastro-resistant pellets containing - in addition to an inert nucleus, a layer with the active compound and an outer enteric layer - one or more intermediate layers (c), placed between the layer with the active compound and the enteric layer. Said layer (c) comprises: (i) an inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients; and (ii) a system of modified release that comprises an inert, non-alkaline polymer

soluble in water and an inert polymer insoluble in water.

As demonstrated in the examples of the present invention, the pellets are able to provide slow or very slow release profiles of the active compound, very suitable for the oral administration of acid labile benzimidazole compounds.

As stated above, U.S. Patent No. 5,945,124 and U.S. Patent No. 6,068,856 do not teach or suggest one more or more intermediate layers that comprise an inert, non-alkaline coating formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients and a system of modified release that comprises an inert non-alkaline polymer soluble in water and an inert polymer insoluble in water as defined in the present invention.

Furthermore, the presence of the layer (c) as described above in the pellet of the present invention, makes it unnecessary to have the alkaline compounds in direct or intimate mixture with the acid labile benzimidazole compounds in the pellets of the present invention. This is reflected in the claims and description of the present invention.

There are, therefore, two different approaches for the stabilization of the acid labile benzimidazole compounds present in the pellets. Thus, while U.S. Patent No. 5,945,124 and U.S. Patent No. 6,068,856 effect a chemical stabilization of the active compound, which is based on the alkaline environment, the present invention effects a physical stabilization, which is provided by the use of the mentioned double intermediate layers (c)(i) and (c)(ii), in particular in the presence of the layer(s) (c)(i), see claim 25 of the present application. It is therefore quite clear that neither U.S. Patent No. 5,945,124 and U.S. Patent No. 6,068,856 teach or suggest employing an additional intermediate layer(s) consisting of an inert, non-alkaline coating formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients.

One skilled in the art at the time of the invention would not look to combine the teachings of U.S. Patent No. 5,945,124 and U.S. Patent No. 6,068,856 with the teachings of U.S. Patent No. 5,445,829.

U.S. Patent No. 5,445,829 describes an extended release pharmaceutical formulation in the form of particles, which are formed by a core and a coating of extended release. The formulation described in U.S. Patent No. 5,445,829 comprises from 0 to 50% of an immediate release particle containing a core of at least one drug, and up to 100% of extended release particles. The immediate release particles contain a core of at least one drug, inert spherical substrate particle and binder which is coated with talc; while the extended release particles are additionally coated with a dissolution modifying system containing plastercizers and a film former agent.

The particles of U.S. Patent No. 5,445,829 do not have an enteric coating as described in U.S. Patent No.'s 5,945,124 and 6,068,856. Therefore, the active ingredient of U.S. Patent No. 5,445,829 is released in the stomach and not in the small intestine like the pellets described in U.S. Patent No.'s 5,945,124 and 6,068,856. This difference is considered to be very important because the release of the formulations described in U.S. Patent No. 5,445,829 in the stomach would have a different effect than the release of the formulations in the small intestine as described in U.S. Patent No.'s 5,945,124 and 6,068,856.

Moreover, the technical problem to be solved by U.S. Patent No. 5,445,829 is to provide an extended release pharmaceutical formulation capable of releasing drugs, selected from a wide variety of active compounds, independently if they are not acid labile compounds, over a 12 to at least a 24 hour period, while the problem to be solved by U.S. Patent No.'s 5,945,124 and 6,068,856 is to provide a stable or oral pharmaceutical composition of an acid labile compound which also provides a release control.

Therefore, U.S. Patent No. 5,445,829 on the one hand, and U.S. Patent No.'s 5,945,124 and 6,068,856 on the other are both confronted with very different problems and provide, accordingly, very different solutions.

Therefore, one skilled in the art at the time of the invention would not look to combine the cited prior art references to make the pellet with the system of modified release of the present invention.

The study of the inventive activity of the present invention effected by the Examiner

can only be seem as a case of ex post facto analysis. Moreover, the Examiner did not consider the objective teaching of each document. It appears that the Examiner just picked up those parts of the disclosures of the cited documents which were useful to eventually mosaic the present invention.

According to MPEP 2141 when applying 35 U.S.C. §103, the following tenets of patent law must be adhered to:

> (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and (D) reasonable expectation of success is the standard with which obviousness is determined.

In making this rejection, the Examiner is relying on impermissible hindsight.

A reference must be considered for what it would teach someone skilled in the art at the time the invention was made and not be applied based on "hindsight". See Panduit Corp. V. Dennison Manufacturing Co. 227 USPQ 337, 343 (Fed. Cir. 1985):

> It is impermissible to first ascertain factually what applicants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct appellants' invention from such prior art.

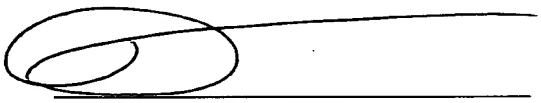
In making its obviousness determination, a court must view the prior art without reading into that art the patent's teachings. Vandenberg v. Dairy Equipment, 224 U.S.P.Q. 195 (Fed. Cir. 1987) citing In re Sponnoble, 160 U.S.P.Q. 237 (CCPA 1969). In Uniroyal v. Rudkin-Wiley, 50 U.S.P.Q.2d 1434, 1438 (Fed. Cir. 1988) the CAFC stated:

> The obviousness standard, while easy to expound, is sometimes difficult to apply. It requires the decision maker to return to the time the invention was made. The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time...That which may be clear and thus obvious to a court, with the invention fully diagramed and aided by experts in the field, may have been a breakthrough of substantial dimension when first unveiled [citations omitted]. In this case we are convinced that the district court misapplied the obviousness standard. It has impermissibly used hindsight to reconstruct the claimed invention

from prior art with the invention before it and aided by Uniroyal's expert, rather than viewing the invention from the position of a person of ordinary skill at the time it was made. When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself.

In light of the above, Applicants submit that all rejections of record have been overcome. Applicants accordingly submit that the application is now in condition for allowance and respectfully request action in accordance therewith.

Respectfully submitted,



JANET I. CORD
LADAS & PARRY
26 West 61st Street
New York, NY 10023
Reg. No. 33,778 (212) 708-1935

MARKED-UP COPY

SPECIFICATION:

- - The pellets of the invention can be administered in an appropriate pharmaceutical formulation, such as a solid pharmaceutical formulation, suitable for oral administration, for example, in the form of hard gelatin capsules or they may be formulated as tablets. The pharmaceutical formulation may contain pellets with different profiles of modified release, that is to say, with systems of modified release that have a differently weighted ratio (insoluble polymer: soluble polymer), for example, they may contain a mixture of (i) pellets with a fast release profile and (ii) pellets with a slow release profile, in a ratio (i):(ii), by weight, lying between 5:95 and 95:5, preferably 10:90 and 90:10. The pellets with a slow release profile comprise a ratio of insoluble polymer: soluble polymer in the system of modified release greater than in the case for pellets with a fast release profile. In the sense used in this description, the term "pellets with a slow release profile" refers to pellets that release in aqueous medium, pH 6.8, after 30 minutes [that is to say, 150 minutes if the 2 hours in acid medium (HCl) are counted according to Monograph 724 of the USP for "Drug Release", in particular, for Delayed-Release (Enteric coated Articles)] a maximum of 50% of the active ingredient. If the amount of active ingredient release in such conditions is greater than 50% then said pellets are considered, for the purposes of this specification, as "pellets with a fast release profile". Example 8 shows some illustrative data of pellets with slow release profiles and fast release profiles according to the present invention. - -

CLAIMS

21. (Twice Amended) A composition of modified release [according to claim 20] comprising a mixture of the [wherein the one or more] pellets of claim 25 having [have] the same release profile [of the benzimidazole].

22. (Twice Amended) A composition of modified release [according to claim 20,] comprising a mixture of the [wherein the one or more] pellets of claim 25 having [have] a different release profile [of the benzimidazole].

23. (Twice Amended) A composition of modified release [according to claim 20, further] comprising a mixture of [(i)] the pellets of claim 25 which have (i) [with] a quick release

profile and (ii) [pellets with] a slow release profile in a ratio between 10:90 and 90:10 by weight.

25. (Amended) A pellet comprising an acid labile benzimidazole compound, wherein the pellet comprises:

(a) an inert nucleus;

(b) a layer disposed over said inert nucleus (a), comprising an acid labile benzimidazole compound, an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients;

(c) one or more intermediate layers that comprise:

(i) an inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients; and

(ii) a system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert polymer insoluble in water;

said intermediate layer(s) (c) disposed over said layer (b) that covers the inert nucleus; and

(d) an external layer comprising an enteric coating disposed over said intermediate layer(s) (c).